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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,760	AUSTIN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-66* is/are pending in the application.

4a) Of the above claim(s) *18-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 12/12/02, as Paper No. 12. Claims 1-17 have been cancelled. New claims 47-66 have been added. Claims 18-66 are pending in the application. Claims 18-46 have been withdrawn from consideration as being drawn to non-elected invention, as set forth in the previous Office Action. Claims 47-66 are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Drawings

As mentioned in the previous Office Action, the drawings are considered informal. Formal drawings need to be filed upon notice of allowance. Specifically, Figures 2 and 7 are too dark and the details of the photographs cannot be discerned.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 47-54 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The instant claims are drawn to a method of inhibiting the generation of active

thrombin on the surface of a cell within an athersclerotic plaque within a mammal, the method comprising producing an ER resident chaperone protein in said cell. The omitted steps are: the steps which lead to the production of the ER resident chaperone in the cell. Without a clear indication of the method steps which result in production of an ER resident chaperone in the cell, the method is unclear and indefinite. Indicating that a nucleic encoding and expressing GRP78/BiP is transferred to the cells or indicating that interleukin-3 is administered to the cells would obviate this rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 47-54 and 60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between

function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

The instant claims encompass administering to the cell a compound which induces the expression or activation of an endogenous ER resident chaperone protein (see claims 47-54 and 60). Therefore the claims encompass a genus of possibly thousands of different compounds, considering every possible compound which could induce the expression or activation of any endogenous ER resident chaperone protein, such as: small molecules, transcription factors, nucleic acid molecules which encode a chaperone or which encode inducers or activators of the chaperone, as well as peptides and proteins which can induce chaperone expression or activation. The specification only indicates that a cytokine or a nucleic acid encoding an ER resident chaperone protein can be used to activate a chaperone or induce chaperone expression. Therefore, the specification has only explicitly discloses two species of molecules which can induce ER resident chaperone expression or activate an ER resident chaperone out of a genus that has possibly thousands of different species. Furthermore, there is no indication of the chemical structures that would be common to all of the compounds encompassed by the claims. Therefore, there is an insufficient description of the compounds encompassed by the claims and one of skill in the art would not be able to recognize any of the claimed compounds (other than the two explicitly disclosed) without performing additional experimentation to determine which compounds induced chaperone expression or activated the chaperone(s).

7. Claims 47-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the generation of active thrombin on the surface of a cell within a mammal wherein said method comprises directly administering to said cell a polynucleotide which encodes and expresses GRP78/BiP, whereby GRP78/BiP is produced in said cell and the generation of active thrombin on the surface of said cell is inhibited;

AND

A method for inhibiting the generation of active thrombin on the surface of a cell within an atherosclerotic plaque within a mammal wherein said method comprises administering to said cell interleukin-3 whereby the generation of active thrombin on the surface of said cell is inhibited;

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the method commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods for inhibiting the generation of active thrombin on the surface of cells in a mammal by administering a compound or a nucleic acid encoding an

ER resident chaperone protein to said cell. Therefore the nature of the invention encompasses gene therapy.

The breadth of the claims

The broadest claims encompass administering any compound which increases the expression of any ER resident chaperone protein or any compound which activates ER resident chaperone protein (see claim 47 and 60). Claim 61 only limits the compound to any cytokine. The broadest claims also encompass administering a nucleic acid which encodes and expresses any ER resident chaperone protein to the target cell by any means of administration such as systemic administration.

The unpredictability of the art and the state of the prior art

Regarding the administration of a nucleic acid encoding a gene of interest to a cell in a mammal (i.e. gene therapy), it is well established in the art that delivery is one of the key problems. For instance, regarding gene therapy in general, Anderson (Nature 1998; 392(suppl):25-30) teaches,

> The challenge is to develop gene therapy as an efficient and safe drug delivery system. The goal is more difficult to achieve than many investigators had predicted... The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. (See p. 25, second paragraph). The ultimate goal of gene therapy research is the development of vectors that can be injected, will target specific cells, will result in safe and efficient gene transfer into a high percentage of those cells, will insert themselves into appropriate regions of the genome (or will persist as stable episomes), will be regulated be either by administered agents or by the body's own physiological signals, will be cost effective and will cure disease. (See p. 30, first paragraph).

Crystal (Science 1995; 270:404-410) also indicates some of the problems associated with gene therapy in general, including problems associated with delivery. Specifically, regarding the

obstacles of human gene transfer, Crystal teaches, "The [gene transfer] vector (should) be specific for its target, not recognized by the immune system..." (See p. 409, column 2 under "The perfect vector").

Finally, regarding the delivery of gene therapy vectors to tumors, but applicable to the specific delivery of all gene therapy molecules, Greco (Frontiers in Biosci. 2002; 7:d1516-1524) teaches,

> The administration of gene therapy vectors requires that they be not only targeted, but also protected from degradation, sequestration or immune attack, in order to reach the appropriate sites for transfection. Although some success has been reported for naked DNA, efficient delivery has been restricted to intratumoral injection. (See p. 1517, paragraph bridging columns 1-2).

Indicating that direct delivery of the nucleic acid to the desired site of transfection is critical for delivering the nucleic acid to the appropriate target cells.

Regarding the administration of a nucleic acid which encodes and expresses any ER resident chaperon protein in order to inhibit the generation of active thrombin on the surface of the cell, it is noted that the prior art does not teach that a ER resident chaperone proteins are associated with the generation of active thrombin on the surface of cells. Therefore, without evidence indicating a sufficient number of ER chaperone proteins can inhibit the generation of active thrombin on the surface of a cell, it is unpredictable that any ER chaperone protein could inhibit the generation of active thrombin on the surface of a cell.

Regarding the administration any compound which increases the expression of any ER resident chaperone protein or any compound which activates ER resident chaperone protein, it is noted that the only compound which has been identified by the prior art as capable of inducing the expression of an ER resident chaperone protein is interleukin-3, which has been shown to

induce GRP78/BiP expression in cells (see Brewer, listed in the IDS as Citation No. 1). The claims also encompass the administration of any cytokine to induce ER resident chaperone protein expression. However, the only cytokine which has been demonstrated to induce any ER resident chaperone protein expression is IL-3. Considering that cytokines are a diverse genus of molecules with extremely divers functions (such as pro-inflammatory cytokines and anti-inflammatory cytokines), it is highly unlikely that that all cytokines would induce ER resident chaperone expression. There is no indication in the relevant art that any compound or cytokine other than IL-3 (a pro-inflammatory cytokine) could induce expression of any ER resident chaperone protein. Therefore, without evidence indicating which compounds and cytokines activate the expression of ER resident chaperone proteins, it is unpredictable that any compound (or any cytokine other than IL-3) could activate expression of ER chaperone protein in a cell and inhibit the generation of active thrombin on the surface of the cell.

Working Examples and Guidance in the Specification

The specification discloses that expression of recombinant GRP78/BiP (an ER resident chaperone protein) inhibits the generation of active thrombin on the surface of cells (in vitro). There is no disclosure indicating that any ER resident chaperone protein other than GRP78/BiP is capable of inhibiting the generation of active thrombin on the surface of a cell. Considering that ER resident chaperone proteins have different functions (such as Calcium regulation, protein folding, and protein transport) it is unpredictable which ER resident chaperone proteins could inhibit the generation of active thrombin on the surface of a cell.

There is no disclosure in the specification which overcomes the problems regarding gene delivery recognized in the art. Therefore, it is unpredictable that the nucleic acid of interest

could be administered by any means other than direct administration to the target cells and result in the transfection of the proper target cells. It is unpredictable that the nucleic acid of interest could be administered systemically to a mammal and result in the specific transfection of the target cells.

The specification does not disclose that any compound or any cytokine other than IL-3 can be used to activate the expression of any ER resident chaperone protein. Furthermore, the specification and the prior art (Brewer) indicate that IL-3 can activate the expression of GRP78/BiP.

Quantity of Experimentation

Considering the breadth of the claims, the unpredictable nature of the invention, and the limited guidance provided in the specification, additional experimentation would be required in order to practice the methods to the full scope encompassed by the claims. For instance, additional experimentation would be required to overcome the problems associated with systemic delivery of a nucleic acid to a target cell, additional experimentation would also have to be performed in order to determine if all ER resident chaperone proteins could inhibit the generation of active thrombin and if all cytokines could activate the expression of all ER resident chaperones (only a sufficient number of cytokines and ER resident chaperones would have to be demonstrated).

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the unpredictable nature of the invention, the limited guidance provided in the specification and the high degree of skill required to practice the claimed methods, additional experimentation would be required in order to use the invention to the full scope encompassed by the claims. Based on the evaluation of all of the Wands factors, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

All of the previous pending elected claims have been cancelled. Furthermore the new claims encompass limitations which overcome the rejection of the previous claims under 35 USC 102. However, the new claims still encompass the delivery of a nucleic acid encoding a gene of interest to specific target cells in a mammal by administering the nucleic acid by any means (such as systemic administration). As mentioned above, the claims are only enabled for delivering the nucleic acid of interest by directly administering the nucleic acid to the target cells.

Applicant's arguments filed 12/12/02 as they pertain to the enablement rejection as it would pertain to the new claims have been fully considered but they are not persuasive. Applicants argue that they have cited a number of references which indicate that the nucleic acid of interest can be delivered to target cells in vivo.

In response, it is acknowledged that the nucleic acid of interest can be administered to a target cell in vivo, but only by directly administering the nucleic acid to the target cell in vivo,

not by systemic delivery of the nucleic acid, for the reasons set forth above. The references cited by the applicants does not overcome the problems associated with systemic delivery mentioned above.

The previous rejection of claims under 35 USC 112, first paragraph for an insufficient written description of variant ER resident proteins (i.e. any variant or derivative of a ER resident chaperone protein) is withdrawn in view of applicants arguments. However, a new rejection has been has been applied for the insufficient description of the compounds which can induce ER resident chaperone expression or activate an ER resident chaperone for the reasons set forth above.

The previous rejection of claims under 35 USC 112, second paragraph are withdrawn in view of the amendments. However, a new rejection has been applied for the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
February 24, 2003

DAVE T. NGUYEN
PRIMARY EXAMINER